CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-017

21-018

ADMINISTRATIVE DOCUMENTS

30 Page(s) Redacted

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

1 of

Application:

NDA 21017/000

Priority: 34S

- Org Code: 510

Stamp: 22-DEC-1998 Regulatory Due: 22-OCT-1999

Action Goal:

Applicant:

District Goal: 23-AUG-1999

Page

LILLY

Brand Name:

HUMALOG MIX 25 (INSULIN LISPRO

LILLY CORPORATE CENTER

25% INJ/I

INDIANAPOLIS, IN 46285

Established Name:

Generic Name: INSULIN LISPRO 25% INJ/INSULIN

LISPRO 75

Dosage Form:

INJ (INJECTION)

Strength:

100 U/ML

FDA Contacts:

H. RHEE

(HFD-510)

301-827-6424 , Project Manager

, Review Chemist

S. MOORE

(HFD-510)

301-827-6430 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1819470

ELI LILLY AND CO

DMF No:

AADA No:

LILLY CORP CTR/WHITE RIVER PK

INDIANAPOLIS, IN 46200

Profile: SVS

_OAI Status: NONE

Responsibilities: FINISHED DOSAGE

MANUFACTURER

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-MAR-1999 **ACCEPTABLE**

Decision: Reason:

DISTRICT RECOMMENDATION

Establishment: 9610945

DMF No: AADA No:

LILLY FRANCE SA

RUE DE COLONEL LILLY B P 10

FEGERSHEIM,, FR

Profile: SVS

OAI Status: NONE

Responsibilities: FINISHED DOSAGE MANUFACTURER

Last Milestone: OC RECOMMENDATION

Decision:

Milestone Date: 03-MAR-1999 **ACCEPTABLE**

Reason:

DISTRICT RECOMMENDATION

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Page 1 of

Application: NDA 21018/000

Stamp: 22-DEC-1998 Regulatory Due: 22-OCT-1999

Priority: 34S

Org Code: 510

Action Goal:

District Goal: 23-AUG-1999

Applicant:

LILLY

Brand Name:

HUMALOG MIX 50 (INSULIN LISPRO

50% INJ/I

LILLY CORPORATE CENTER

INDIANAPOLIS, IN 46285

Established Name:

Generic Name: INSULIN LISPRO 50% INJ/INSULIN

LISPRO 50

Dosage Form: INJ (INJECTION)

Strength:

100 U/ML

FDA Contacts:

H. RHEE

(HFD-510)

301-827-6424 , Project Manager

, Review Chemist

S. MOORE

(HFD-510)

301-827-6430 , Team Leader

Overall Recommendation:

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Milestone Date: 03-MAR-1999

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: NDA 21018/000 Priority: 34S

Org Code: 510

HUMALOG MIX 50 (INSULIN LISPRO

Stamp: 22-DEC-1998 Regulatory Due: 22-OCT-1999

INDIANAPOLIS, IN 46285

Action Goal: Brand Name: District Goal: 23-AUG-1999

Applicant: LILLY

LILLY CORPORATE CENTER

Established Name:

Generic Name: INSULIN LISPRO 50% INJ/INSULIN

LISPRO 50

50% INJ/I

Dosage Form: INJ (INJECTION)

Strength:

100 U/ML

FDA Contacts: H. RHEE

(HFD-510)

301-827-6424 , Project Manager

W. BERLIN

(HFD-510)

301-827-6370 , Review Chemist

S. MOORE

(HFD-\$10)

301-827-6430 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAR-1999 by J. D AMBROGIO (HFD-324)301-827-0062 ---

Establishment: 1819470

DMF No:

ELI LILLY AND CO

AADA No:

LILLY CORP CTR/WHITE RIVER PK

INDIANAPOLIS, IN 46200

Profile: SVS

OAI Status: NONE

Responsibilities: FINISHED DOSAGE MANUFACTURER

Last Milestone: OC RECOMMENDATION

Milestone Date 03-MAR-1999

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

Establishment: 9610945

LILLY FRANCE SA

DMF No: AADA No:

RUE DE COLONEL LILLY B P 10

FEGERSHEIM, FR

Profile: SVS

OAI Status: NONE

Responsibilities: FINISHED DOSAGE

MANUFACTURER

Last Milestone: OC RECOMMENDATION Milestone Date 03-MAR-1999

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:

NDA 21017/000

Priority: 34S

Org Code: 510

Stamp: 22-DEC-1998 Regulatory Due: 22-OCT-1999

Action Gozl:

LILLY

District Goal: 23-AUG-1999 **HUMALOG MIX 25 (INSULIN LISPRO**

Applicant:

LILLY CORPORATE CENTER

Brand Name: 25% INJ/I

INDIANAPOLIS, IN 46285

Established Name:

Generic Name: INSULIN LISPRO 25% INJ/INSULIN

LISPRO 75

Dosage Form: INJ (INJECTION)

Strength:

100 U/MIL

FDA Contacts:

H. RHEE

(HFD-510)

301-827-6424 , Project Manager

W. BERLIN

(HFD-510)

301-827-6370 , Review Chemist

S. MOORE

(HFD-510)

301-827-6430 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAR-1999by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1819470

DMF No:

ELI LILLY AND CO

AADA No:

LILLY CORP CTR/WHITE RIVER PK

INDIANAPOLIS, IN 46200

Profile: SVS

OAl Status: NONE

Responsibilities: FINISHED DOSAGE MANUFACTURER

MANUFACTURER

Last Milestone: OC RECOMMENDATION

Milestone Date 03-MAR-1999

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

Establishment: 9610945

LILLY FRANCE SA

DMF No: AADA No:

RUE DE COLONEL LILLY B P 10

FEGERSHEIM,, FR

Profile: SVS

OAT Status: NONE

Responsibilities: FINISHED DOSAGE

Last Milestone: OC RECOMMENDATION

Milestone Date 03-MAR-1999

ACCEPTABLE

Decision: Renson:

DISTRICT RECOMMENDATION

BEST POSSIBLE COPY

CERTIFICATION

NDA Application No.: NDA 21-017

Drug Name: Humalog® Mix25

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

Gregory G. Enge Ph. D.

Title: Director, U.S. Regulatory Affairs

Date: December 21, 1998

CERTIFICATION

NDA Application No.: NDA 21-018

Drug Name: Humalog® Mix50

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: XIIIII D

Title: Director, U.S. Regulatory Affairs

Date: December 21, 1998

PEDIATRIC PAGE
(Complete for all original application and all efficacy supplements)

			
NDA/BLA Number:	<u>21017</u>	Trade Name:	HUMALOG MIX 25 (INSULIN LISPRO 25% INJ/I
Supplement Number:		Generic Name:	INSULIN LISPRO 25% INJ/INSULIN LISPRO 75
Supplement Type:		Dosage Form:	Injectable; Injection
Regulatory Action:	<u>AP</u>	Proposed Indication:	Treatment of patients with diabetes mellitus for the control of hyperglycemia.
Nec	ENDED Nates ((Pediatric Age Gro	oups for this submission? hildren (25 Months-12 years) dolescents (13-16 Years)
Label Adequacy Formulation Status Studies Needed		s Not Apply NEW FORMULAT	CION is needed
Study Status			
Are there any Pediatric	Phase 4 C	ommitments in the A	ction Letter for the Original Submission? NO
COMMENTS:	·		
his Paga was samulas i	·.		
ULIE RHEE	no Desec on	iniormation from a F	PROJECT MANAGER/CONSUMER SAFETY OFFICER,
/S/	/		12-10-99
Signature			Date
•			

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21018	Trade Name:	HUMALOG MIX/50 (INSULIN LISPRO 50%
Supplement Number:		Generic Name:	INSULIN LISPRO 50% INJ/INSULIN LISPRO 50
Supplement Type:		Dosage Form:	Injectable; Subcutaneous
Regulatory Action:	<u>AP</u>	Proposed Indication:	Treatment of patients with diabetes mellitus for the control of hyperglycemia.
:	:		
NO, No waiver and	no pedia	atric data	HIS SUBMISSION?
Ne Infa	oN āt es (i antš (1-2	0-30 Days)C 4 Months)A	Children (25 Months-12 years) Adolescents (13-16 Years)
Label Adequacy Formulation Status Studies Needed Study Status	<u> NO</u>	s Not Apply NEW FORMULA further STUDIES a	
are there any Pediatric	Phase 4 (Commitments in the A	action Letter for the Original Submission? NO
	<u>:</u>	•	
his Page was completed ULIE RHEE	d based or	n information from a	PROJECT MANAGER/CONSUMER SAFETY OFFICER,
Signature	<i>ـــلوــــ</i> ـــــــــــــــــــــــــــــ		/2-10-99 Date

RE: NDA #s 21017 and 21018 Insulin Lispro Mixtures and Pediatric Studies

The vast majority of pre-pubescent children with diabetes and many post pubescent teens with diabetes have Type 1 diabetes. The DCCT has shown that long-term complications of Type 1 diabetes can be prevented with intensive insulin therapy. (Subsequent data suggest that intensive therapy can also benefit Type 2 patients.) Fixed ratios of insulin products do not permit frequent dose adjustment and tight control-especially in those without endogenous insulin production. The use of such fixed ratio mixtures cannot be recommended in patients with Type 1 diabetes—especially children. Therefore pediatric studies have not been requested.

Elizabeth Koller, M.D.

12/17/99

APPEARS THIS WAY ON ORIGINAL

('C: On, DDAS 21-017 + 21-018 HFD-510/Div Files 21-017 + 21-018 HFD-510/Koller

Exclusivity Checklist

NDA: 21-018				
Trade Name: Humalog Mix 50/50				
Generic Name: 50% insulin lispro protamine suspension and 50% insulin lispro (rDNA or	igin) ini	ction		
Applicant Name: Eli Lilly	-E7 9		-	
Division: Division of Metabolic and Endocrine Drug products, HFD-510				
Project Manager: Julie Rhee, 7-6424				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEED	ED?	_		
1. An exclusivity determination will be made for all original applications, but only	for co-	tain	Sunnle	ments
Complete raits if and iff of this exclusivity Summary only if you answer "yes"	' to on	e or	more	of the
to low ling questions about the submission.				
a. Is it an original NDA?	Yes	х	No	T
b. Is it an effectiveness supplement?	Yes	П	No	х
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change			T	
in labeling related to safety? (If it required review only of bioavailability or	Yes	х	Νo	}
bioequivalence data, answer "no.")	<u> </u>		<u> </u>	
If your answer is "no" because you believe the study is a bioavailability study and, the exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for dis	refore,	not e	ligibl	e for
arguments made by the applicant that the study was not simply a bioavailability study	agreem	g wi	h any	'
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness				 -
change or claim that is supported by the clinical data:	uppien	ieni,	aescri	be the
Explanation:				
d. Did the applicant request exclusivity?	Yes	Г	No	Τx
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	1103		pvo	<u> </u>
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS. O	ODIB	E C T	1- V: 7	
THE SIGNATURE BLOCKS.	O DIN	LCI	LII	U
2. Has a product with the same active ingredient(s), dosage form, strength, route of			T-	
administration, and dosing schedule previously been approved by FDA for the same	Yes		No	x
ise?			1	:
f yes. NDA #				
Orug Name:				
F THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGN	ATUR	E BI	OCI	ćS.
is this drug product or indication a DESI upgrade?	Yes		No	х
F THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGN	ATUR	E BI	OCK	S
even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL E	NTITI	ES		
Answer either #1 or #2, as appropriate)				
. Single active ingredient product.	Yes		No	
las FDA previously approved under section 505 of the Act any drug product				
ontaining the same active moiety as the drug under consideration? Answer "yes" if			1	j
ne active moiety (including other esterified forms, salts, complexes, chelates or lathrates) has been previously approved, but this particular form of the active moiety,	Yes		No	x
g., this particular ester or salt (including salts with hydrogen or coordination		į	I	.
, Jack the state of the state o	<u>, </u>	1		1

bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate)	T	T	7	T
has not been approved. Answer "no" if the compound requires metabolic conversion	ł		1	
(other than deesterification of an esterified form of the drug) to produce an already	ł			
approved active moiety.		1	1	ì
If "yes," identify the approved drug product(s) containing the active moiety, and, if kn	own, t	ne NI)A #(<u>!</u> s).
Drug Product	T			
NDA#	†	-		
Drug Product	†			
NDA#	 			
Drug Product	 			
NDA#	`			
2. Combination product.	Yes	x	No	
If the product contains more than one active moiety (as defined in Part II, #1), has	 	 	1	├──
FDA previously approved an application under section 505 containing any one of the	1			
active moieties in the drug product? If, for example, the combination contains one	l	1	1	
never-before-approved active moiety and one previously approved active moiety,	Yes	X	No	
answer "yes." (An active mojety that is marketed under an OTC monograph, but that		1	1	İ
was never approved under an NDA, is considered not previously approved.)	1		1	
If "yes," identify the approved drug product(s) containing the active moiety, and, if kn	own, th	e ND)A #(s	·).
Drug Product: Humalog			· · · ·	
NDA # 20-563				
Drug Product	 			
NDA#		<u> </u>		
Drug Product	<u> </u>			
NDA#				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIR	ECTL'	Y TO	·THE	
SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
			-	
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPI	EME	NTS		
To qualify for three years of exclusivity, an application or supplement must contain "re	POTIS C	fnev	v clini	cal
investigations (other than bioavailability studies) essential to the approval of the applic	ation a	nd co	nduct	ed or
sponsored by the applicant." This section should be completed only if the answer to PA	ART II.	Oues	tion 1	or 2
was "yes."	ŕ			
1. Does the application contain reports of clinical investigations? (The Agency				
interprets "clinical investigations" to mean investigations conducted on humans other	1			
han bioavailability studies.) If the application contains clinical investigations only by	1 1			
	Yes	x	No	
'yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation				
eferred to in another application, do not complete remainder of summary for that	1			
nvestigation.	i	1		
F "NO." GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have ap	proved	the a	polic	ation
or supplement without relying on that investigation. Thus, the investigation is not essen	itial to	the ar	יייייייי	il if
) no clinical investigation is necessary to support the supplement or application in ligh	t of pre	viou	slv	''
pproved applications (i.e., information other than clinical trials, such as bioavailability	data v	would	l be	
ufficient to provide a basis for approval as an ANDA or 505(b)(2) application because	of wha	at is a	iready	,
mown about a previously approved product), or 2) there are published reports of studie	s (othe	r than	those	. 1
onducted or sponsored by the applicant) or other publicly available data that independ	ently w	ould	have !	been I

the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.						
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement	Yes	×				
If "no." state the basis for your conclusion that a clinical trial is not necessary for ap DIRECTLY TO SIGNATURE BLOCKS.	proval A	ND GO	·			
Basis for conclusion:						
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	x N	lo			
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. If yes, explain:	Yes	N	0	'x		
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes	N	0			
lf yes, explain:						
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigation application that are essential to the approval:	ns subm	itted in t	he			
Investigation #1, Study #: IODK						
Investigation #2, Study #: IODM						
Investigation #3, Study #: IODN	<u> </u>					
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.						
a) For each investigation identified as "essential to the approval," has the investigation	ם been re	lied on	hv t	he		
agency to demonstrate the effectiveness of a previously approved drug product? (If the relied on only to support the safety of a previously approved drug, answer "no.")	e investi	igation v	vas			
investigation #1	Yes	No	7	$\overline{\mathbf{x}}$		
Investigation #2	Yes	No		X		
Investigation #3	Yes	No	7	Ţ		
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:						
Investigation #1 NDA-Number	T			_		
Investigation #2 NDA Number	1			\dashv		
Investigation #3 NDA Number						
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?						
Investigation #1	Yes	No	1	x		
Investigation #2	Yes	No	 -	×		
Investigation #3	Yes	No		X		

If you have answered "yes" for one or more investigations, identify the NDA in which was relied on:	a sim	ilar iz	rvesti	gation
Investigation #1 NDA Number				
Investigation #2 NDA Number	 			
Investigation #3 NDA Number	 		-	
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the applica	<u> </u>			
is essential to the approval (i.e., the investigations listed in #2(c), less any that are not	tion or "new")	supp):	lemer	it that
Investigation #1 エロアド				
Investigation #2 ±0D M				
Investigation #3 ZODN				
4. To be eligible for exclusivity, a new investigation that is essential to approval must conducted or sponsored by the applicant. An investigation was "conducted or sponsor before or during the conduct of the investigation, 1) the applicant was the sponsor of the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest support for the study. Ordinarily, substantial support will mean providing 50 percent of study. a. For each investigation identified in response to question 3(c): if the investigation was	ed by" he IND st) prov er more	the a nam ided of th	pplica ied in subst ie cost	the antial t of the
IND, was the applicant identified on the FDA 1571 as the sponsor?	.s cuiii			CI dii
Investigation #1	Yes		No	x
IND#:				
Explain: Study conducted outside the U.S.				
Investigation #2	Yes		No	X
IND#:			`	,
Explain: Study conducted outside U.S.				
Investigation #3	Yes		No	x
IND#:				
Explain: Study conducted outside U.S.	<u> </u>	, - _		
b. For each investigation not carried out under an IND or for which the applicant was responsor, did the applicant certify that it or the applicant's predecessor in interest provide for the study?	ot ider led sub	ntifie stant	d as thial sup	ne oport
	Yes	х	No	
IND#:				
Explain:	·			
Investigation #2	Yes	х	No	
ND#:			-	
Explain:				
Investigation #3	Yes	х	No	
ND#:				
Explain:				
Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe hat the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all ights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
f yes, explain:				f

Julie Rhee
Project Manager

cc:OrigNDA HFD-510/DivFile HFD-93/Holovac Solomon Sobel, M.D.
Division Director

Exclusivity Checklist

PADA: 21-017				
Trade Name: Humalog Mix 75/25				
Generic Name: 75% insulin lispro protamine suspension and 25% insulin lispro (rDNA or	igin) ini	ection	l	
Applicant Name: Eli Lilly	<u> </u>			
Division: Division of Metabolic and Endocrine Drug products, HFD-510				
Project Manager: Julie Rhee (7-6424)	<u> </u>			
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEED	ED?			
1. An exclusivity determination will be made for all original applications, but only	for cor	tain	supple	ments
Complete Parts II and III of this Exclusivity Summary only if you answer "yes"	to on	e or	more	of the
following questions about the submission.				0. 4.0
a. Is it an original NDA?	Yes	T x	No	T
b. Is it an effectiveness supplement?	Yes	1	No	X
c. If yes, what type? (SE1, SE2, etc.)	7	<u> </u>	-	<u>,</u>
Did it require the review of clinical data other than to support a safety claim or chang	:	ī	1	T
in labeling related to safety? (If it required review only of bioavailability or	Yes	x	No	·
bioequivalence data, answer "no.")	1	l		1
If your answer is "no" because you believe the study is a bioavailability study and, the	refore,	not e	ligibl	e for
exclusivity, EXPLAIN why it is a bloavailability study, including your reasons for dis	agreein	ıg wi	th any	•
arguments made by the applicant that the study was not simply a bioavailability study				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness	upplen	ient,	descri	be the
change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	х
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	1			
IF YOU HAVE ANSWERED "NO" TO <u>ALL</u> OF THE ABOVE QUESTIONS, OF THE SIGNATURE BLOCKS.	O DIR	ECT	LYI	0
	,			
2. Has a product with the same active ingredient(s), dosage form, strength, route of	L.			
administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	х
f yes, NDA #	 -		<u> </u>	<u> </u>
Orug Name:				
F THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGN 3. Is this drug product or indication a DESI upgrade?		E B	_	ζS.
	Yes		No	X
F THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGN even if a study was required for the upgrade).	ATUR	E B	LOC	cs
was required for the appraise).				
PART II. FIVE VEAR EVELUEIUTV FOR NEW CURNICAL R				— -
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL E Answer either #1 or #2, as appropriate)	NTITII	ES		
Single active ingredient product.				
	Yes	· .	No	×
las FDA previously approved under section 505 of the Act any drug product ontaining the same active moiety as the drug under consideration? Answer "yes" if	[]			
the active moiety (including other esterified forms, salts, complexes, chelates or	Yes		L.	
lathrates) has been previously approved, but this particular form of the active mojety	1 62		No	×
.g., this particular ester or salt (including salts with hydrogen or coordination				ĺ
	—			

bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.				
	<u> </u>	<u> </u>	<u> </u>	<u> </u>
If "yes," identify the approved drug product(s) containing the active moiety, and, if kn Drug Product	own, the	he NI)# AC	s).
NDA #	-			
	ļ			
Drug Product	1			
NDA#	<u> </u>			
Drug Product	<u> </u>			
NDA#				
2. Combination product.	Yes	Х	No	
If the product contains more than one active moiety (as defined in Part II, #1), has — FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known	own, th	e NE)A #(s).
Drug Product: Humalog				<u> </u>
NDA # 20-563				
Drug Product	_			
NDA#	_			
Drug Product	-			
NDA#				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIR SIGNATURE BLOCKS. IF "YES," GO TO PART III.	ECTL	Y TO	THE	
5,		,,		
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPI	EME	NTS		
To qualify for three years of exclusivity, an application or supplement must contain "re investigations (other than bioavailability studies) essential to the approval of the applic sponsored by the applicant." This section should be completed only if the answer to PA was "yes."	ation a	nd co	nduct	ed or l
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	x	No	
IF "NO." GO DIRECTLY TO THE SIGNATURE BLOCKS.	<u>'</u>			
2. A clinical investigation is "essential to the approval" if the Agency could not have approved in the content without relying on that investigation. Thus, the investigation is not essent in a clinical investigation is necessary to support the supplement or application in light approved applications (i.e., information other than clinical trials, such as bioavailability sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because known about a previously approved product), or 2) there are published reports of studies.	tial to t of products, v data, v of what s (other	the aperious would at it as a than the state of the state	oprova sly l be dready	al if
conducted or sponsored by the applicant) or other publicly available data that independ	ently w	ould	have	been

the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies. a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS. Basis for conclusion: b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicity available data would not independently support approval of the application? 1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. If yes, explain: 2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? If yes, explain: c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the applicant on that are esseftival to the approval: Investigation #1, Study #: IODM Investigation #2, Study #: IODM J. In addition to being essential, investigations must be "new" to support exclusivity. The agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product; (i.e., does not referemonstrate something the agency to demonstrate the investi								
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Investigation #2 - Yes No x	drug product?	p		, ~PP	-, -, -,			
Investigation #2 - Yes No x	investigation #1	Yes		No	×			
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Investigation #3 Yes No x		Yes			Y			

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Investigation #1 NDA Number	7			
Investigation #2 - NDA Number	╁			
Investigation #3 - NDA Number	┼			
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the applica	<u> </u>			0 ah a
is essential to the approval (i.e., the investigations listed in #2(c), less any that are not	"new"	չսին):	iemen	it that
Investigation #1 FODK	T	-		
Investigation #2 IODM	1			
Investigation #3 IOPN	1			
4. To be eligible for exclusivity, a new investigation that is essential to approval must conducted or sponsored by the applicant. An investigation was "conducted or sponsor before or during the conduct of the investigation, 1) the applicant was the sponsor of t form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interesupport for the study. Ordinarily, substantial support will mean providing 50 percent of study.	ed by" he IND st) prov or more	the ap nam rided of th	oplica ed in subst e cost	the antial of the
a. For each investigation identified in response to question 3(c): if the investigation was IND, was the applicant identified on the FDA 1571 as the sponsor?	is carri	ed ou	t unde	ran
Investigation #1	Yes		No	×
IND#:		-		1
Explain: Study conducted outside the U.S.	-			
Investigation #2	Yes		No	x
IND#:	 		,	
Explain: Study conducted outside the U.S.				
Investigation #3	Yes	Г	No	x
IND#:	 		.	
Explain: Study conducted outside the U.S.	<u> </u>			
b. For each investigation not carried out under an IND or for which the applicant was a sponsor, did the applicant certify that it or the applicant's predecessor in interest provide for the study?	iot ider led sub	ntified stanti	as that	e port
Investigation #1	Yes	х	No	
ND#:			•	
Explain:			•	
nvestigation #2	Yes	х	No	
ND#:				
Explain:				
nvestigation #3	Yes	х	No	
ND#:	<u> </u>			
Explain:				
Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe hat the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all ights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	x
f yes, explain:				

Page 5 NDA 21-017

Jylie Rhee
Project Manager

/S/
Solomon Sobel, M.D.
Division Director

CC: Ong NDA

HFD-510/Div File

HFD-93/May Ann Holovae

PATENT INFORMATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Humalog Mix50TM [50% insulin lispro injection and 50% insulin lispro protamine suspension (r-DNA origin)], as indicated. This product is the subject of this application for which approval is being sought:

Patent No.	Expiration Date	Claim Type
5,461,031	June 16, 2014	formulation, method of use
5,474,978	June 16, 2014	formulation
5,514,646	May 7, 2013	formulation, composition, method of use
5,747,642	June 16, 2014	formulation

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana

EXCLUSIVITY

Eli Lilly and Company (Lilly) does not claim the three-year period of exclusivity for the use of Humalog Mix50TM [50% insulin lispro injection and 50% insulin lispro protamine suspension (r-DNA origin)] in the treatment of Diabetes Mellitus provided by 21 C.F.R. 214.108 (b)(5)

Date: December 21, 1998

Gregory G. Enas, Ph.D.

Director

U.S. Regulatory Affairs Eli Lilly and Company

PATENT INFORMATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Humalog Mix25TM [25% insulin lispro injection and 75% insulin lispro protamine suspension (r-DNA origin)], as indicated. This product is the subject of this application for which approval is being sought:

Patent No.	Expiration Date	Claim Type
5,461,031	June 16, 2014	formulation, method of use
5,474,978	June 16, 2014	formulation
5,514,646	May 7, 2013	formulation, composition, method of use
5,747,642	June 16, 2014	formulation

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

EXCLUSIVITY

Eli Lilly and Company (Lilly) does not claim the three-year period of exclusivity for the use of Humalog Mix25TM [25% insulin lispro injection and 75% insulin lispro protamine suspension (r-DNA origin)] in the treatment of Diabetes Mellitus provided by 21 C.F.R. 314.108 (b)(5).

Gregory G. Enas, Ph.D.

Director

U.S. Regulatory Affairs

Eli Lilly and Company

APPEARS THIS WAY ON ORIGINAL

Date: December 21, 1998